U.S. FOOD & DRUG ADMINISTRATION

Memorandum

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To: Memo to Docket No. FDA-2014-Q-1146 ("Petition for a Health Claim for Eicosapentaenoic Acid and Docosahexaenoic Acid and Reduction of Blood Pressure in the General Population")

Subject: Review of Scientific Literature on Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA) Intake and Risk of Excessive Bleeding

Background

This memorandum reviews the scientific literature on the effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on risk of excessive bleeding. EPA and DHA are omega-3 fatty acids commonly used in dietary supplements. They are also components of some fatty fish, fish oils, other foods (e.g., seaweed), and food ingredients (e.g., algal oils). This review is part of the safety assessment the Food and Drug Administration (FDA or we) is conducting in the context of its evaluation of a petition for qualified health claims in the labeling of conventional foods and dietary supplements (see 21 CFR 101.14(b)(3)(ii)). The requested claims are about possible benefits of EPA and DHA intake in reducing the risk of hypertension and coronary heart disease by lowering blood pressure. Because dietary supplements containing EPA and DHA have become available in higher doses and with higher levels of daily intake recommended on their labels since FDA's last review of a qualified health claim petition for EPA and DHA in 2004, this review focuses on the effects of consuming more than 3 grams per day of EPA and DHA in combination on risk of excessive bleeding. We limited our review to studies that provided more than 3 grams per day of EPA and DHA because intake below this level does not cause an increase in bleeding time[1] and is not considered to increase the risk of excessive bleeding (see 62 FR 30751 at 30752-53; June 5, 1997).

In 1997, FDA issued a final rule affirming that menhaden oil is generally recognized as safe (GRAS) as a food ingredient with specific limitations on use to ensure that the total daily intake of EPA and DHA from conventional foods does not exceed 3 grams per person per day (g/p/d) (62 FR 30751; June 5, 1997) (codified as amended at 21 CFR 184.1472). Although the use

[1] Bleeding time is a medical test that measures how fast small blood vessels in the skin stop bleeding. https://medlineplus.gov/ency/article/003656.htm (accessed 05/13/19)

limitations in this rule apply only to conventional foods and not to dietary supplements, the scientific evidence considered in the rulemaking is relevant in both contexts. The 1997 final rule discussed the Agency's review of the scientific evidence publicly available at that time regarding the possible contribution of fish oil consumption to increased bleeding time, reduced glycemic control in non-insulin dependent diabetics (type II diabetes), and increased low-density lipoprotein (LDL) cholesterol (62 FR 30752 to 30754).[2] With regard to bleeding time, FDA concluded:

> In summary, the totality of the scientific evidence demonstrates that when consumption of fish oils is limited to 3 g/p/d or less of EPA and DHA, there is no significant risk for increased bleeding time beyond the normal range. ... On the other hand, amounts of fish oils providing more than 3 g/d of EPA and DHA have generally been found to produce increases in bleeding time that are statistically significant. At this time, there are insufficient data to evaluate the clinical significance of this bleeding. Because of the lack of data and because of the potential risk of excessive bleeding in some individuals with intakes at higher levels, FDA concludes that the safety of menhaden oil is generally recognized only at levels that limit intake of EPA and DHA to 3 g/p/d.
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> 62 FR at 30753.

In recent years, the use of bleeding time to evaluate the risk of excessive bleeding has been discredited and discontinued in clinical practice because technical limitations of this test render it inaccurate (Ref. 1-4). Studies that describe subjects' history of excessive bleeding or evaluate clinical outcomes such as periprocedural[3] bleeding episodes or blood loss are more useful to evaluate the risk of excessive bleeding (Ref. 1-4). This review focuses on studies that reported data on excessive bleeding events (e.g., hemorrhagic stroke) after intake of EPA and DHA because those studies provide the most clinically relevant information.

There is no current regulatory limit on the amount of EPA and DHA in dietary supplements, and dietary supplements are now available with combined EPA and DHA content over 8 g/day. The purpose of this memorandum is to summarize and assess the current evidence on the effects of EPA and DHA on risk of excessive bleeding, as measured by clinical outcomes such as bleeding episodes and blood loss. Evidence on the effects of EPA and DHA on glycemic control and blood cholesterol is discussed in a separate memo[4].

This review includes only original studies published since FDA's evaluation of evidence about bleeding risk for the 1997 GRAS final rule on the use of menhaden oil as a food ingredient.

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[2] In 2005, FDA amended the GRAS affirmation regulation to reallocate the maximum levels of menhaden oil in various categories of conventional food but did not change the 3 g/day GRAS limit on total intake of EPA and DHA from conventional foods. See 70 Fed. Reg. 14531 (March 23, 2005).

[3] Occurring soon before, during, or soon after a medical procedure. https://www.merriam-webster.com/medical/periprocedural (accessed June 3, 2019)

[4] See Memo to Docket No. FDA-2014-Q-1146. "Survey of Comprehensive Reviews of the Effects of Eicosapentaenoic Acid (EPA) and Docosahexaenoic acid (DHA) Intake on Glycemic Control and Blood Cholesterol." (June 17, 2019).

Because the most recent publication listed as a reference in that rule was published in 1993, we considered only articles published after 1993 in our current evaluation.

Search Strategy and Method

On January 31, March 4, 27, and 28, 2019, queries of PubMed and Embase were conducted to identify clinical trials with data on the effects of EPA and DHA intake on risk of excessive bleeding. PubMed and MEDLINE are databases maintained by the U.S. National Library of Medicine (NLM). PubMed includes over 29 million citations from the biomedical literature[5]. Embase is a biomedical database that covers over 8,500 journals from over 95 countries and is produced by Elsevier[6]. Search terms for EPA and DHA ("eicosapentaenoic acid", "docosahexaenoic acid," "DHA", "EPA", "fish oil", "omega-3 fatty acids", or "cod liver oil") were combined with those for bleeding ("bleeding", "international normalized ratio" [7] [a measure of blood clotting time], "surgery and bleeding," or "hemostasis"[8]). A total of 2,712 references were identified at the conclusion of the search.

References that were duplicates, animal studies, not in English, not related to the topic, not randomized controlled clinical trials[9], did not conduct appropriate statistical analysis between the treatment and control, or were published prior to 1994 were excluded from further review. The remaining abstracts were reviewed to identify articles to include in this review. References for relevant articles were hand-searched for additional studies to include in the review.

A total of 6 studies were examined to determine if there is a relationship between ingesting more than 3 g/day of omega-3 fatty acids and risk of excessive bleeding. The range of doses provided in these studies was 3.32 to 5.4 g/day.

Clinical Studies That Measured a Bleeding-Related Clinical Outcome

In 1996, Eritsland and colleagues published the results of a study that randomized 610 participants into 4 groups to determine if the consumption of fish oil would reduce the rate of restenosis in subjects who had undergone coronary artery bypass graft (CABG) surgery (Ref. 5). The first group of 148 participants received aspirin 300 mg/day, the second group of 143 participants received aspirin 300 mg/day and fish oil (3.32 g/day of EPA and DHA), the third group of 145 participants received warfarin 15 mg /day, and the fourth group of 174 participants received warfarin (an anticoagulant) 15 mg/day and fish oil (3.32 g/day of EPA and DHA). For the purposes of analysis, the data from the aspirin only group and warfarin only group were combined into a single control group (293 subjects total). The fish oil plus aspirin group and fish oil plus warfarin group were also combined into a single fish oil group (317 subjects total).

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[5] http://www.ncbi.nlm.nih.gov/pubmed (accessed 5/10/19)

[6] https://www.elsevier.com/solutions/embase-biomedical-research (accessed 5/10/19)

[7] When the international normalized ratio is higher than the recommended range, it means that your blood clots more slowly than desired, and a lower INR means your blood clots more quickly than desired. https://www.mayoclinic.org/tests-procedures/prothrombin-time/about/pac-20384661 (accessed 05/15/19)

[8] Hemostasis is the process that stops blood loss from a damaged blood vessel. *See* Blanco A, Blanco G. 2017. Medical Biochemistry. Chapter 31, Hemostasis. Academic Press, San Diego, CA, p. 781.

[9] Randomized clinical trials minimize bias by assigning study participants to a control or a treatment group and by blinding participants and researchers who analyze the results of the study to assess the effects of the treatment. See Spilker B. 1991. Guide to Clinical Studies. Raven Press, New York, New York.

There was no statistically significant difference in the total number of bleeding episodes between the fish oil and control groups (34 vs 27, p=0.22). The study is limited by insufficient information about the types and doses of medications being taken in each group.

In 1996, Cairns and colleagues published results of their study comparing the effects of fish oil and low molecular weight heparin (LMWH), an anticoagulant, on the reduction of restenosis[10] of coronary arteries after percutaneous transluminal coronary angioplasty (PTCA) (Ref. 6). Subjects were initially randomized into 2 groups; the first group received 5.4 g/d of EPA and DHA combined, and the second received corn oil placebo (control). The fish oil and corn oil capsules were consumed for not less than 7 days before PTCA and continued for 4 months. At the end of 4 months, subjects with residual coronary artery stenosis (blockage) less than 50% were randomized to receive either subcutaneous injections of LMWH 30 mg twice a day or standard therapy[11] (control) for the next 4 months, in addition to what they had been taking during the first phase of the study (fish oil or corn oil placebo). The remaining subjects (those with 50% residual stenosis or more) did not continue with the study after the initial 4-month treatment period. During the second 4-month phase of the study, there were four groups: corn oil alone (control), corn oil plus LMWH (control), fish oil alone, and fish oil plus LMWH. The two corn oil control groups (328 subjects total) and the two fish oil treatment groups (325 subjects total) were combined for analysis. Six hundred and fifty-three subjects completed the study. At the end of the study, the authors found that the occurrence of bleeding was lower in the subjects taking fish oil (5.2% of 325) than in those taking corn oil placebo (11.6% of 328). This difference between groups was statistically significant ($p<0.05$). Bleeding was characterized by bruising and peri-procedural bleeding consisted of excessive oozing at the femoral puncture site. Most bleeding was mild, leading to permanent discontinuation of study medication in only six (0.9%) of the subjects[12], and no subject needed a transfusion due to bleeding. Study limitations: Although the authors reported the medical conditions of the subjects at the beginning of the study, they did not provide information regarding any of the medications a subject was taking before or during the study.

In 1999, von Schacky and colleagues published a report regarding the effects of EPA and DHA on coronary atherosclerosis (Ref. 7). In this study, 23 subjects with angiographically proven coronary artery disease were randomized into two groups. One group received a placebo for 24 months. The other group received 3.4 g/day of EPA and DHA for the first 3 months and then 1.7 g/day EPA and DHA for the remaining 21 months. Subjects underwent coronary angiography at baseline and 24 months later. One of the subjects in the fish oil group experienced a hemorrhagic event (stroke) with minimal residual neurologic disability. The authors attributed the stroke to inadequately treated hypertension, not to fish oil. The authors also reported that minor hematoma was observed with the follow-up angiography. Unfortunately, the authors did not provide information as to which group of subjects experienced the hematoma.

In 2002, the main results of the Esapent for Prevention of Restenosis ITalian Study (EPRITS) were published (Ref. 8). This double-blind, placebo-controlled trial was designed to determine if

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[10] Recurrent blockage of the artery.

[11] The article did not provide any details about the standard therapy.

[12] The article did not specify which group or groups these six subjects belonged to.

omega-3 fatty acids could prevent restenosis in coronary arteries post-PTCA. The authors randomized 339 subjects to receive either 3 g/day EPA and 2.1 g/day DHA (total of 5.1 g/day) or an olive oil placebo for 1 month before and 1 month after PTCA. Subjects in the EPA and DHA group then continued half the dose for six months; the placebo group was given olive oil for the same amount of time. All subjects received either aspirin (100 to 500 mg/d) or indobufen (200 mg twice a day), an antiplatelet agent, for 48 hours prior to PTCA and for a minimum of 15 days after the PTCA. After that treatment, antiplatelet therapy was given at the discretion of the patient's physician. In the 257 subjects who qualified for follow-up (125 in the omega 3 fatty acid group and 132 in the placebo group), 9 subjects had periprocedural bleeding after PTCA. Of these 9 subjects, 6 (2.1%) were in the omega-3 fatty acid group and 3 (1%) in the placebo group. This difference in periprocedural bleeding between the two groups was not statistically significant. The authors stated that "A reassuring confirmation from our study was the lack of any significant side effect of the active treatment, either on bleeding … or other monitored end points." The major problem with interpreting the study's results with regard to bleeding is that it is not possible to determine the dose and duration for which a patient received antiplatelet therapy.

In 2011, Farquharson and colleagues published a study that examined the effect of dietary fish oil (4.6 g/day of EPA and DHA) on atrial fibrillation after cardiac surgery (Ref. 9). Two hundred subjects were randomized to receive 4.6 g/day of EPA and DHA or a sunflower oil placebo. Subjects started taking the oils 3 weeks prior to surgery and continued until 6 days after surgery or until discharge. Ninety-seven subjects in the EPA and DHA group and 97 subjects in the sunflower oil group were included in the intention to treat analysis. The medications and medical conditions were similar in both groups at baseline. Major bleeding episodes occurred in 8 (8%) of the sunflower oil group and 3 (3%) of the EPA and DHA group ($p=0.21$) but there was no statistically significant difference between the two groups. The authors stated that there was no statistically significant difference between groups regarding adverse events and no difference between groups in blood loss through the chest drains ($p=0.39$). A large proportion of subjects in the control group (43%) lost more red blood cells than in the EPA and DHA group (26%), and the difference between groups was statistically significant ($p=0.02$). The study results are noteworthy because if fish oil increases the risk of bleeding, one would expect the fish oil group to lose a greater amount of blood and red blood cells than the control group.

In 2016, Heydari and colleagues published a randomized, placebo-controlled study that examined the effect of omega-3 acid ethyl ester on left ventricular remodeling after acute myocardial infarction (heart attack) over a 6-month period (Ref. 10). One hundred eighty subjects received 2.4 g/day of linoleic acid and 178 received 3.36 g/day of EPA and DHA. The authors reported that no subject experienced significant bleeding related to the study drug; however, it is unclear if they were referring to statistical or clinical significance. Additionally, the authors reported that 8 of the 11 subjects who died during the study were in the fish oil group. None of the 8 patients who died experienced any bleeding during the 6 months of fish oil treatment.

Conclusion

Our review identified six studies that evaluated bleeding-related clinical outcomes at doses between 3.36 g/day to 5.4 g/day of EPA and DHA. None of these studies showed an increase in bleeding events (Ref. 5-10). Based on the evidence from these clinical trials that measured clinical outcomes such as bleeding episodes and blood loss, we conclude that consumption of EPA and DHA at levels up to approximately 5 g/day does not increase the risk of excessive bleeding.

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